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LETTER TO THE EDITOR

Skin pain and sleep quality numeric rating scales for children aged 6 months to 5 years with atopic dermatitis

Dear Editor,

Skin pain and sleep disturbances are key symptoms of atopic dermatitis (AD) that profoundly impact patient quality of life.[1,2] Although skin pain and sleep numeric rating scales (NRS) have been validated for adolescents/adults with AD,[3–5] no skin pain or sleep scale instruments have been validated for children (6 months to 5 years) with AD. For children unable to self-report symptoms, US Food and Drug Administration supports using observer-reported outcomes on clinical outcome assessments.[6,7] We aimed to develop

TABLE 1 Skin Pain numeric rating scale: Convergent/discriminant validity and responsiveness correlations.

	Correlation coefficient[a] (95% CI) (*n*)		
	Convergent/discriminant validity		Responsiveness
	Baseline	Week 16	Change from baseline to week 16
Caregiver-reported outcomes			
WSI-NRS	0.70* (0.61, 0.77) (158)	0.89* (0.85 to 0.92) (136)	0.91* (0.87, 0.93) (135)
Sleep quality NRS	−0.24* (−0.38, −0.09) (158)	−0.52* (−0.63, −0.38) (131)	−0.43* (−0.56, −0.28) (130)
CGID	0.38* (0.24, 0.51) (158)	0.70* (0.60, 0.77) (136)	0.64* (0.52, 0.73) (135)
CGIC	NA[b]	NA[b]	0.55* (0.42, 0.65) (135)
SCORAD itch VAS	0.43* (0.29, 0.55) (158)	0.79* (0.71, 0.84) (135)	0.68* (0.57, 0.76) (134)
SCORAD sleeplessness VAS	0.34* (0.20, 0.47) (158)	0.64* (0.52, 0.73) (135)	0.60* (0.47, 0.69) (134)
POEM itchy skin	0.04 (−0.11, 0.20) (158)	0.57* (0.44, 0.67) (136)	0.52* (0.38, 0.63) (135)
POEM total	0.34* (0.20, 0.47) (158)	0.67* (0.56, 0.75) (136)	0.63* (0.51, 0.72) (135)
IDQoL itching/scratching	0.26* (0.04, 0.46) (75)	0.73* (0.57, 0.83) (55)	0.51* (0.27, 0.68) (55)
IDQoL total	0.21 (−0.02, 0.42) (75)	0.71* (0.54, 0.82) (55)	0.56* (0.34, 0.71) (55)
Patient-reported outcomes			
CDLQI itchy/scratchy/sore/painful	0.37* (0.17, 0.54) (83)	0.63* (0.48, 0.75) (80)	0.47* (0.26, 0.63) (72)
CDLQI sleep affected	0.15 (−0.07, 0.35) (83)	0.52* (0.34, 0.66) (80)	0.50* (0.30, 0.66) (72)
CDLQI total	0.35* (0.14, 0.52) (83)	0.59* (0.42, 0.71) (80)	0.60* (0.42, 0.73) (72)
Clinician-reported outcomes			
SCORAD objective	0.16* (0.00, 0.31) (158)	0.60* (0.48, 0.70) (135)	0.51* (0.37, 0.62) (134)
EASI total	0.12 (−0.03, 0.27) (158)	0.51* (0.38, 0.63) (136)	0.41* (0.26, 0.54) (135)
IGA	−0.01 (−0.17, 0.14) (158)	0.48* (0.34, 0.60) (136)	0.41* (0.26, 0.54) (135)

Abbreviations: CDLQI, Children's Dermatology Life Quality Index; CGIC, Caregiver Global Impression of Change; CGID, Caregiver Global Impression of Disease; CI, confidence interval; EASI, Eczema Area and Severity Index; IDQoL, Infants' Dermatitis Quality of Life Index; IGA, Investigator Global Assessment; NRS, Numeric Rating Scale; POEM, Patient-Oriented Eczema Measure; SCORAD, SCORing Atopic Dermatitis; VAS, Visual Analog Scale; WSI-NRS, worst scratch/itch Numeric Rating Scale.

*$p < 0.05$ (Pearson correlation).

[a]Correlations of <0.3 were considered small, 0.3 to <0.7 moderate, 0.7 to <0.9 strong and ≥0.9 very strong.

[b]Due to CGIC being impression of change from baseline to week 16.

Clinical Trial Registration: ClinicalTrials.gov Identifier: NCT03346434.

and validate a caregiver-reported Skin Pain and Sleep Quality NRS for young children with moderate-to-severe AD, and derive meaningful within-patient change (MWPC) thresholds.

The Skin Pain NRS item was based on standard cognitive debriefing methodology for caregivers to rate their child's worst skin pain. The Sleep Quality NRS item was adapted from an unpublished sleep quality item for adults with AD.

Content validity was assessed through three rounds of concept elicitation and cognitive-debriefing interviews with caregivers of children (6 months to 5 years) with moderate-to-severe AD. Psychometric evaluation[6–8] was conducted using data from LIBERTY AD PRESCHOOL part B (NCT03346434),[9] a 16-week, randomized, double-blind, placebo-controlled, phase 3 study of dupilumab in children (6 months to 5 years) with AD ($n = 161$; mean age 3.9 years). Distribution-based methods were analysed using baseline score and intra-class coefficients (ICCs). Written institutional review-board-approved informed consent and verbal consent were obtained from trial and interview participants, respectively. Both instruments are available online (https://eprovide.mapi-trust.org/).

TABLE 2 Sleep Quality numeric rating scale: Convergent/discriminant validity and responsiveness correlations.

	Correlation coefficient[a] (95% CI) (*n*)		
	Convergent/discriminant validity		Responsiveness
	Baseline	Week 16	Change from baseline to week 16
Caregiver-reported outcomes			
WSI-NRS	−0.34* (−0.47, −0.19) (159)	−0.54* (−0.65, −0.41) (131)	−0.44* (−0.56, −0.28) (131)
Worst skin pain NRS	−0.24* (−0.38, −0.09) (158)	−0.52* (−0.63, −0.38) (131)	−0.43* (−0.56, −0.28) (130)
Sleep diary			
Difficulty falling asleep (h)	−0.20* (−0.35, −0.05) (159)	−0.24* (−0.39, −0.07) (132)	−0.20* (−0.36, −0.03) (132)
Night-time awakenings (h)	−0.47* (−0.58, −0.34) (156)	−0.60* (−0.70, −0.47) (123)	−0.48* (−0.61, −0.33) (120)
Number of night-time awakenings	−0.54* (−0.64, −0.42) (158)	−0.57* (−0.68, −0.44) (125)	−0.55* (−0.66, −0.41) (124)
Sleep duration (h)	0.26* (0.11, 0.40) (159)	0.26* (0.10, 0.41) (132)	0.29* (0.12, 0.44) (132)
CGID	−0.31* (−0.45, −0.17) (159)	−0.52* (−0.63, −0.38) (132)	−0.39* (−0.52, −0.23) (132)
CGIC	NA[b]	NA[b]	−0.27 (−0.42, −0.10) (132)
SCORAD sleeplessness VAS	−0.33* (−0.46, −0.18) (159)	−0.52* (−0.64, −0.38) (131)	−0.35* (−0.49, −0.18) (131)
SCORAD itch VAS	−0.28* (−0.42, −0.13) (159)	−0.50* (−0.62, −0.36) (131)	−0.35* (−0.49, −0.19) (131)
POEM itch	−0.07 (−0.22, 0.09) (159)	−0.47* (−0.59, −0.32) (132)	−0.26* (−0.41, −0.09) (132)
POEM total	−0.24* (−0.38, −0.08) (159)	−0.48* (−0.60, −0.34) (132)	−0.41* (−0.54, −0.26) (132)
IDQoL getting to sleep	−0.08 (−0.30, 0.15) (75)	−0.40* (−0.60, −0.15) (54)	−0.27* (−0.50, 0.00) (54)
IDQoL sleep disturbance	−0.21 (−0.42, 0.01) (75)	−0.41* (−0.61, −0.16) (54)	−0.26 (−0.49, 0.01) (54)
IDQoL itching/scratching	−0.25* (−0.45, −0.02) (75)	−0.48* (−0.66, −0.24) (54)	−0.24 (−0.47, 0.04) (54)
IDQoL total	−0.31* (−0.50, −0.09) (75)	−0.55* (−0.71, −0.32) (54)	−0.30* (−0.52, −0.03) (54)
Patient-reported outcomes			
CDLQI sleep affected	−0.42* (−0.58, −0.23) (84)	−0.51* (−0.66, −0.33) (77)	−0.43* (−0.60, −0.21) (72)
CDLQI itchy/scratchy/sore/painful	−0.22* (−0.41, 0.00) (84)	−0.52* (−0.66, −0.33) (77)	−0.40* (−0.57, −0.18) (72)
CDLQI total	−0.51* (−0.65, −0.33) (84)	−0.52* (−0.66, −0.33) (77)	−0.51* (−0.66, −0.32) (72)
Clinician-reported outcomes			
SCORAD objective	−0.21* (−0.35, −0.06) (159)	−0.57* (−0.68, −0.44) (131)	−0.33* (−0.47, −0.17) (131)
EASI total	−0.18* (−0.32, −0.02) (159)	−0.53* (−0.64, −0.39) (132)	−0.26* (−0.41, −0.09) (132)
IGA	NA[c]	−0.48* (−0.60, −0.34) (132)	−0.25* (−0.40, −0.08) (132)

Abbreviations: CDLQI, Children's Dermatology Life Quality Index; CGIC, Caregiver Global Impression of Change; CGID, Caregiver Global Impression of Disease; CI, confidence interval; EASI, Eczema Area and Severity Index; IDQoL, Infants' Dermatitis Quality of Life Index; IGA, Investigator Global Assessment; NRS, Numeric Rating Scale; POEM, Patient-Oriented Eczema Measure; SCORAD, SCORing Atopic Dermatitis; VAS, Visual Analog Scale; WSI-NRS, worst scratch/itch Numeric Rating Scale.

*$p < 0.05$ (Spearman correlation for sleep diary items; Pearson correlation for all other items).

[a]Correlations of <0.3 were considered small, 0.3 to <0.7 moderate, 0.7 to <0.9 strong, and ≥0.9 very strong.

[b]Due to CGIC being changed from baseline to week 16.

[c]Due to baseline requirement for IGA ≥3.

Caregivers (mean age 34 years) found Skin Pain ($n = 24$) and Sleep Quality NRS ($n = 15$) to be clear and understandable. Skin Pain NRS asked caregivers to rate their child's skin pain at its worst during the previous 24 h from 0 (no pain) to 10 (worst pain possible). Sleep Quality NRS asked caregivers to select a number from 0 (worst possible sleep) to 10 (best possible sleep) to describe the quality of their child's sleep during the previous night.

Among 65 patients with no change in Caregiver Global Impression of Disease (CGID) from baseline to week 2 in LIBERTY AD PRESCHOOL, test–retest reliability ICC for weekly Skin Pain NRS (0.68; 95% CI: 0.50, 0.80) approached the accepted ≥0.70 criterion for adequate reliability.[8] The Sleep Quality NRS (0.80; 95% CI: 0.69, 0.87) exceeded the criterion.

Skin Pain NRS scores demonstrated moderate/strong correlations with caregiver/patient-reported outcomes at week 16 (r [95% CI] = 0.52 [0.43, 0.66] to 0.89 [0.85, 0.92]) (Table 1) and lower correlations with clinician-reported outcomes (r [95% CI] = 0.48 [0.34, 0.60] to 0.60 [0.48, 0.70]). Sleep Quality NRS scores showed moderate correlations with caregiver/patient-reported and clinician-reported outcomes at week 16 (Table 2; $r = -0.41$ [−0.61, −0.16] to −0.60 [−0.70, −0.47]), but weaker correlations with sleep duration and difficulty falling asleep ($r = 0.26$ [0.10, 0.41] and −0.24 [−0.39, −0.07]).

Correlations of change from baseline were moderate/strong between Skin Pain NRS and patient/caregiver- and clinician-reported measures (Table 1; $r = 0.41$ [0.26, 0.54] to 0.91 [0.87, 0.93]) and small/moderate between these measures and Sleep Quality NRS (Table 2; $r = -0.20$ [−0.36, −0.03] to −0.51 [0.66, 0.32]).

The proposed MWPC threshold defining clinical relevance for Skin Pain NRS is a ≥2-point reduction using CGID as the primary anchor. An MWPC threshold for Sleep Quality NRS could not be estimated.

Limitations are inclusion of US-English-speaking caregivers only and using individual items for psychometric analyses not validated for use as single-item instruments. Skin Pain NRS and Sleep Quality NRS were well understood and moderately reliable caregiver-reported instruments in children aged 6 months to 5 years with moderate-to-severe AD. These instruments could be incorporated into future clinical trials and clinical practice to fully assess treatment effects in young children with AD.

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CONFLICT OF INTEREST STATEMENT

AS Paller has been an investigator for AbbVie, Applied Pharma Research, Dermavant, Eli Lilly, Incyte, Janssen, Krystal, Regeneron Pharmaceuticals Inc., Timber, UCB; consultant for AbbVie, Abeona, Apogee, Arcutis, Aslan, BioCryst, Boehringer Ingelheim, Bristol Myers Squibb, Dermavant, Incyte, Johnson and Johnson, Krystal Biotech, LEO, Mitsubishi Tanabe, Nektar, Primus, Procter and Gamble, Regeneron Pharmaceuticals Inc., Sanofi, Seanergy, TWi Biotech, and UCB; and on the data and safety monitoring board for AbbVie, Abeona and Galderma. EC Siegfried is a consultant for Dermavant, Eli Lilly, Pfizer, Regeneron Pharmaceuticals Inc., and Verrica Pharmaceuticals; a member of the data and safety monitoring board for GSK, LEO Pharma and Novan; and is Principal Investigator in clinical trials for Eli Lilly, Janssen, Regeneron Pharmaceuticals Inc., Stiefel and Verrica Pharmaceuticals. SE Marron is a member of the advisory boards of and consultant with research support and honoraria from AbbVie, Almirall, Amgen, Boehringer Ingelheim, Eli Lilly, Galderma, Janssen, LEO Pharma, Novartis, Regeneron Pharmaceuticals Inc., Roche and Sanofi. Marci Clark, Nimanee Harris, Katherine Kosa, Shanshan Qin and Diane Whalley are employees of RTI Health Solutions, which was retained by Regeneron Pharmaceuticals Inc. to conduct the research that is the subject of this manuscript. Their compensation is unconnected to the studies on which they work. Ashish Bansal, Jingdong Chao and Zhixiao Wang are employees and shareholders of Regeneron Pharmaceuticals Inc. Chien-Chia Chuang is an employee of Sanofi and may hold stock and/or stock options in the company.

DATA AVAILABILITY STATEMENT

Qualified researchers may request access to study documents (including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan) that support the methods and findings reported in this manuscript. Individual anonymized participant data will be considered for sharing once the indication has been approved by a regulatory body, if there is legal authority to share the data and there is not a reasonable likelihood of participant re-identification. Submit requests to https://vivli.org/.

ETHICS STATEMENT

Written institutional review-board-approved informed consent and verbal consent were obtained from trial and interview participants, respectively.

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